1 423 851

PATENT SPECIFICATION

(11) 1 423 851

(21) Application No. 14223/73 (22) Filed 23 March 1973
(31) Convention Application No. 3904/72 (32) Filed 24 March 1972 in
(33) Sweden (SW)
(44) Complete Specification published 4 Feb. 1976
(51) INT CL² C07C 131/08; A61K 31/15, 31/395; C07D 295/12
(52) Index at acceptance
C2C 1175 1204 1341 1532 1562 211 215 221 225 226 227 22X 22Y 246 250 251 255 25Y 290 29X 29Y 30Y 311 313 314 31Y 322 323 32Y 332 334 338 339 346 364 36Y 620 650 697 709 711 718 719 790 79Y LY MV

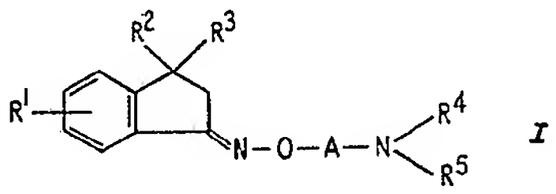
(19)

(54) PHARMACODYNAMICALLY ACTIVE 1,1-DISUBSTITUTED INDANE-3-ONE OXIME DERIVATIVES

(71) We, AKTIEBOLAGET KABI, a Swedish Body Corporate of Lindhagensgatan 133, 112—51 Stockholm, Sweden, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to pharmacodynamically active 1,1 - disubstituted indane - 3 - one - oxime derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

Accordingly, the present invention provides compounds of formula:



I

as well as the corresponding amine oxides, quaternary ammonium compounds and salts with physiologically acceptable acids, wherein in formula I, R^1 represents hydrogen, halogen, an alkoxy group containing 1 to 3 carbon atoms or a nitro group; R^2 and R^3 each represents an alkyl group containing 1 to 3 carbon atoms which may be joined to form, together with the carbon atom in the indane ring to which they are bonded, a ring; A represents an ethylene or trimethylene group or an ethylene or trimethylene group, which is substituted by a lower (as hereinafter defined) alkyl group; and R^4 and R^5 each represents hydrogen or an alkyl group containing 1 to 4 carbon atoms, or together with the amine nitrogen, form a heterocyclic ring, which in addition to the amine nitrogen may contain an oxygen atom or an imino group which may be substituted by a lower alkyl group.

In those cases where the compounds of formula I may occur as optical antipodes, the invention comprises the racemic mixtures as well as each of the components separately. The term "lower" used herein means containing 1 to 6 carbon atoms. Preferred lower alkyl groups are those containing 1 to 3 carbon atoms, and especially the methyl group. The substituent R^1 is preferably in 5′ position. When the substituents R^4 and R^5 together with the amine nitrogen form a heterocyclic ring, the latter is preferably a 5-, 6- or 7-membered ring. Examples of such groups are the pyrrolidino, piperidinyl and morpholino groups.

An interesting subclass of the new compounds of formula I is, for example, such compounds, in which R^2 and R^3 each represents a methyl group or, together with the carbon atom to which they are bonded, form a carbocyclic ring, especially a cyclopentane or a cyclohexane ring. Another interesting subclass of compounds of formula I are those in which R^1 signifies halogen, especially chlorine or fluorine.

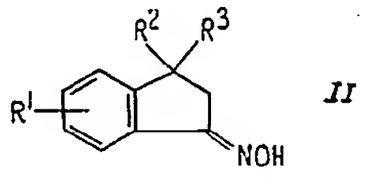
Examples of interesting compounds of formula I are:

3′ - β - dimethylaminoethyl - oximino - spiro-(cyclopentane - 1,1′ - indane),
3′ - β - dimethylaminoethyl - oximino - spiro-(cyclohexane - 1,1′ - indane),
5′ - chloro - 3′ - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1′ indane),
5′ - fluoro - 3′ - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1′ - indane),
3′ - β - methylaminoethyl - oximino - spiro-(cyclopentane - 1,1′ - indane),
1,1 - dimethyl - 3 - β - methylaminoethyl - oximino - indane,

and the corresponding amine oxides, quaternary ammonium compounds and salts with physiologically acceptable acids.

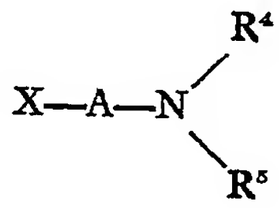
The compounds of formula I are, according to the invention, prepared by the following processes:

1) reacting an indanone oxime of formula:



II

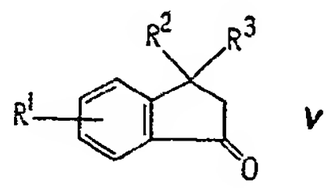
wherein R^1, R^2 and R^3 are as defined above, with a compound of formula:



III

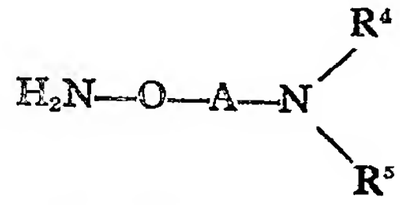
wherein X represents a reactive ester residue and A, R^4 and R^5 are as defined above; or

2) by reacting an indanone of formula:



V

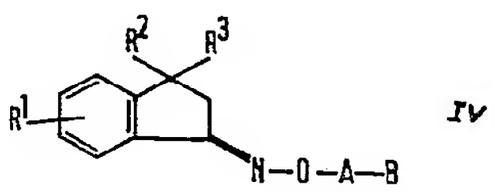
wherein R^1, R^2 and R^3 are as defined above, with a compound of formula:



VI

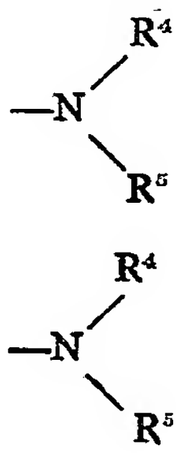
wherein A, R^4 and R^5 are as defined above; or

3) by converting in a manner known *per se* the group B in a compound of formula:



IV

wherein R^1, R^2, R^3 and A are as defined above and B signifies a group convertible in manner known *per se* into the above defined group



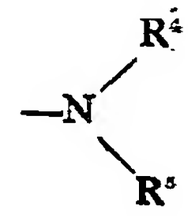
into the group

The term "in a manner known *per se*" as used herein means method heretofore used or described in the chemical literature.

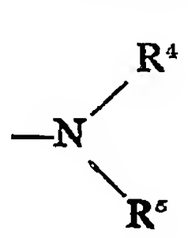
The reaction 1) is preferably carried out in an inert solvent such as dimethylformamide or acetonitrile, the compound of formula II preferably being used as a salt, e.g. with alkali metal ions or quaternary ammonium ions. Halogen-containing groups and arylsulphonyloxy groups are examples of suitable reactive ester residues X.

The reaction 2) is preferably carried out in an inert solvent such as ethanol or pyridine. In this case the compound of formula VI can either be used as the free base or as a salt with an acid. In the latter case the reaction is carried out in the presence of an acid binding agent such as sodium carbonate or pyridine.

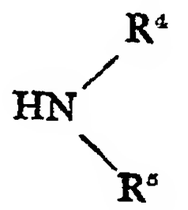
In the method 3), the group B convertible into the group



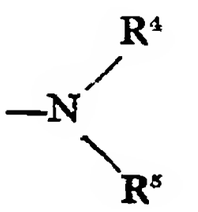
may, for example, be a protected amino group, a hydroxy group, or a reactive ester residue, e.g. a chloride or a bromide. If B is a hydroxy group the conversion into the group



can be carried out by first esterifying the same with an arylsulphonic acid such as benzene- or toluene sulphonic acid, and then reacting the sulphonic acid ester formed with an amine

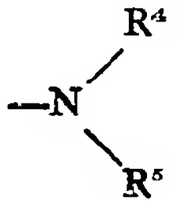


to give the compound of formula I. If B is a halogen atom, the latter can be replaced directly with the amino group



by treatment with the corresponding amine.

Other examples of suitable groups B, which can be converted into the group



by conventional methods, are nitro- or alkoxycarbonylamino groups. The conversion into compounds of formula I is effected by reduction or hydrolysis.

The reactions may also be carried out by first preparing a lower alkylated amine derivative, a primary amine or a secondary amine, which may then be alkylated in a conventional manner to the desired secondary or tertiary amine or quaternary ammonium salt. Furthermore, a tertiary amine can also be dealkylated to the corresponding secondary amine.

The amines of formula I can, if desired, be converted in manner known *per se* into the corresponding salts with physiologically acceptable acids, and the tertiary amines into the corresponding amine oxides.

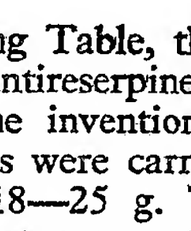
Starting materials or end products, which are mixtures of optical isomers, may be resolved into the pure optical antipodes in conventional manner, for example by fractional crystallisation of diastereoisomeric salts.

Some of the indanones of formula V used as starting compounds in a process of this invention are known compounds. Others are new. The new compounds can be prepared by methods known *per se*, for example according to the general method described by V. Seidlova and M. Protiva [Collection Czechoslovak. Chem. Commun. vol. 32, p.2832 (1967)] which involves heating the acid chlorides of the corresponding substituted β-phenylpropionic acids with polyphosphoric acid. Halogen, alkoxy or nitro substituents R^1 can be introduced into the starting compounds by methods known *per se*.

However, the new compound, spiro(cyclopentane - 1,1′ - indane) - 3′ - one, which is used in the preparation of cyclopentane derivatives of formula I, and the corresponding halogeno, alkoxy and nitro substituted derivatives which are also new compounds, are preferably prepared by a method different to that indicated above, as the compound 1 - phenyl - 1 - cyclopentane - acetic acid, which is then necessary as an intermediate, is difficult to prepare. Spiro(cyclopentane - 1,1′ - indane) - 3′ - one is preferably prepared by the method described in our copending U.K. Patent Application No. 14224/73 (Serial No. 1421208) in which spiro(cyclopentane - 1,1′ - indene) is treated with a hydrogen halogenide, preferably hydrogen chloride, and the 3′ - halogen - spiro(cyclopentane - 1,1′ - indane) compound obtained is oxidised. Then, if desired, a halogen, a C_1—C_3 alkoxy or a nitro substituent R^1 is introduced, in a manner known *per se* into the benzene ring of a reactant of formula II, IV or V or a compound of formula I in which R′ is H. The oxidation is then preferably carried out with chromic acid or an acid chromate solution. By this method the desired indanone is obtained in high yield.

The hydroxy imines of formula II can be prepared from the corresponding indanones of formula V in manner known *per se*, such as is described in Example I below.

The starting compounds of formula IV can be prepared by analogy with the methods 1) and 2) by using compounds which contain in place of the group



a group B convertible into said group.

It has been shown, in animal tests described below, that the compounds of formula I possess valuable pharmacological properties, especially on the central nervous system. In particular they counteract the effect of reserpine, an effect which in pharmacology is used as a measure of the suitability of a compound as a drug against depression. Certain of the compounds of formula I also produce at the same time, antihistamine and/or anticholinergic effects. All the compounds of formula I have low toxicity.

By conventional methods and with the aid of conventional adjuvants, the compounds or salts of this invention can be transformed into suitable pharmaceutical compositions which form a further aspect of the present invention. The compositions may be in the form of e.g. tablets or solutions, preferably in unit dose form, which, for example, can contain between 1 and 500 mg. of the active substance.

In the following Table, the results of tests concerning the antireserpine effect for some compounds of the invention are reported.

All experiments were carried out on albino mice, weighing 18—25 g. The animals had free access to water except during the test period, but were not allowed to eat 4 to 5 hours before the experiment. The substances to be tested were administered orally to the mice in groups of 6, at 4 dosage levels (12.7, 40, 127 and 400 mg/kg.). A control group of 6 mice received water and were observed simultaneously.

After one hour the mice were injected intraperitoneally with 2.5 mg/kg. reserpine, which had been solubilised with a few drops of glacial acetic acid. 0.5, 1, and 2 hours after the treatment with reserpine, the ptosis was measured. A score of 0 means no closure of the eye, 1 for 1/4, 2 for 1/2, 3 for 3/4 and 4 for complete closure. The score varies between 0 and 8 for each mouse (i.e. the sum of score for both eyes of each mouse). The maximum value for 6 mice is thus 48.

The percentages of antagonism for each compound after 0.5, 1 or 2 hours for each dosage group was obtained by comparison with the score of the simultaneously observed control group. The Table indicates the percentage of antagonism after 60 minutes, which is the optimal time for measuring antireserpine effect in this test system.

TABLE

R^1	R^2	R^3	A	$-N\begin{matrix}R^4\\R^5\end{matrix}$	Salt	Antagonism % Dose mg/kg			
						12.7	40	127	400 mg/kg
H	CH_3	CH_3	$-CH_2CH_2-$	$NHCH_3$	Perchlorate	32	77	100	100
H	CH_3	CH_3	$-CH_2CH_2-$	$N(CH_3)_2$	Hydrochloride	35	53	88	–
H	$-(CH_2)_4-$		$-CH_2CH_2-$	$NHCH_3$	Perchlorate	21	93	100	100
H	$-(CH_2)_4-$		$-CH_2CH_2-$	$N(CH_3)_2$	Perchlorate	22	56	100	100
5–Cl	$-(CH_2)_4-$		$-CH_2CH_2-$	$N(CH_3)_2$	Perchlorate	36	43	36	75
5–F	$-(CH_2)_4-$		$-CH_2CH_2-$	$N(CH_3)_2$	Perchlorate				
H	$-(CH_2)_5$		$-CH_2CH_2-$	$N(CH_3)_2$	Perchlorate	36	43	36	75

The following Examples illustrate the invention.

Example 1.

Preparation of starting materials

a) *3' - hydroxyimino - spiro(cyclopentane - 1,1' - indane)*

74.5 g. (0.4 mole) spiro(cyclopentane - 1,1' - indane) - 3' - one, 93.6 g. hydroxylammonium chloride, 172 ml. of pyridine and 440 ml. of ethanol are mixed and refluxed for 3 hours. The mixture is evaporated, 500 ml. of water are added to give a precipitate which is filtered off and dried. The crude oxime obtained is recrystallised from absolute ethanol to give 70 g. (Yield 88%) of colourless crystals melting at 102°C.

In an analogous manner, the following oximes were prepared from the corresponding indanones:

b) *5' - nitro - 3' - hydroxyimino - spiro-(cyclopentane - 1,1' - indane)*, mp. 162°C.

c) *5' - chloro - 3' - hydroxyimino - spiro-(cyclopentane - 1,1' - indane)*, m.p. 140°C.

d) *5' - fluoro - 3' - hydroxyimino - spiro-(cyclopentane - 1,1' - indane)*, m.p. 156°C.

e) *3' - hydroxyimino - spiro(cyclohexane -*

1,1' - indane), m.p. 138—139°C.

f) *1,1 - dimethyl - 3 - hydroxyiminoindane.* Oil, b.p. 120°/0.9 mm.Hg.

g) *5' - methoxy - 3' - hydroxyimino(cyclopentane - 1,1' - indane)*, m.p. 149°C.

Example 2.

a) *3' - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane).*

6 g. (0.03 mole) of 3' - hydroxyimino - spiro(cyclopentane - 1,1' - indane) are added in portions to a solution of 0.77 g. (0.033 gram atoms) of sodium in 150 ml. of absolute ethanol. Then the mixture is refluxed for 1 hour and evaporated *in vacuo*. 20 ml. of dimethylformamide are added to the residue of which 10 ml. are distilled off *in vacuo* to remove any remaining methanol. Another 80 ml. of dimethylformamide are added and then 4.3 g. (0.04 moles) of β - dimethylaminoethyl chloride are added dropwise to the mixture at 25°C. Finally the mixture is heated for 1 hour at 100 to 110°C. The sodium chloride formed is filtered off from the hot solution which is then evaporated to dryness *in vacuo*. The residue is taken up in ether and water, the ether phase is washed with water and dried with anhydrous potassium carbonate.

The perchlorate is obtained if the ether solution of the amine is treated with perchloric acid. After recrystallisation from 2-propanol the salt melts at 136 to 139°C.

In an analogous manner the following substances are prepared from the corresponding oximes and aminoalkyl chloride:

b) *3' - γ - dimethylaminopropyl - oximino - spiro(cyclopentane - 1,1' - indane).* Hydrochloride, m.p. 186 to 187°C.

c) *3' - β - dimethylaminoethyl - oximino - spiro(cyclohexane - 1,1' - indane).* Hydrochloride, m.p. 109 to 112°C.

d) *3' - γ - dimethylaminopropyl - oximino - spiro(cyclohexane - 1,1' - indane)*, m.p. 184°C.

e) *3' - γ - piperidinopropyl - oximino - spiro(cyclohexane - 1,1' - indane).* Hydrochloride, m.p. 176°C.

f) *3' - β - (1 - pyrrolidinyl)ethyl - oximino-spiro(cyclohexane - 1,1' - indane).* Hydrochloride, m.p. 162°C.

g) *3' - β - morpholinoethyl - oximino - spiro(cyclohexane - 1,1' - indane).* Hydrochloride, m.p. 184°C.

h) *3' - β - diethylaminoethyl - oximino - spiro(cyclohexane - 1,1' - indane).* Hydrochloride, m.p. 191°C.

i) *3' - γ - diethylaminopropyl - oximino - spiro(cyclohexane - 1,1' - indane).* Hydrochloride, m.p. 156°C.

j) *1,1 - dimethyl - 3 - β - diethylaminoethyl - oximino - indane.* Hydrochloride, m.p. 138°C.

k) *1,1 - dimethyl - 3 - γ - dimethylaminopropyl - oximino - indane.* Hydrochloride, m.p. 162°C.

l) *1,1 - dimethyl - 3 - γ - piperidinopropyl-oximino - indan.* Fumarate mp. 138°C.

m) *1,1 - dimethyl - 3 - β - (1 - pyrrolidinyl)ethyl - oximino - indane.* Hydrochloride, mp. 157°C.

Example 3.

a) *5' - chloro - 3' - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane).*

5.9 g (0.025 moles) of 5' - chloro - 3' - hydroxyimino - spiro(cyclopentane - 1,1' - indane) are dissolved in 150 ml of dimethylformamide with agitation at room temperature. 2,9 g (0.066 moles) of 55% sodium hydride (dispersed in oil) are added in portions and then the mixture is stirred for 10 minutes at room temperature. 5.1 g (0.035 moles) of dimethylaminoethyl chloride - hydrochloride are added in portions to the mixture which is then stirred for another 10 minutes at room temperature and finally for two hours at 100 to 105°C. The sodium chloride formed is filtered off from the hot solution which is then evaporated. The residue is taken up in ether and water, the ether solution is washed with water and then the amine is extracted with 2 N hydrochloric acid. The acid extract is washed with ether and made alkaline with 40% sodium hydroxide. The free amine is extracted with ether and dried with anhydrous potassium carbonate.

The perchlorate is obtained if the ether solution of the amine is treated with perchloric acid. After recrystallisation from 2-propanol the salt melts at 134°C.

In an analogous manner there is prepared:

b) *5' - fluoro - 3' - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane).* Perchlorate, mp. 172°C.

Example 4.

a) *3' - β - methylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane).*

To a solution of 3' - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane) (33.5 g; 0.11 moles) in dry benzene (120 ml.) is added dropwise during 20 minutes a solution of ethyl chloroformate (24 g; 0.22 moles), and then the mixture is boiled for 2 hours, cooled, washed with 2N hydrochloric acid and dried with anhydrous magnesium sulphate. After evaporation 3' - β - (N - carbethoxy - N - methylamino)ethyl - oximino - spiro(cyclopentane - 1,1' - indane) is obtained as a yellow oil (32.7 g.) which is used in the hydrolysis step without any particular purification.

3' - β - (N - carbethoxy - N - methylamino)ethyl - oximino - spiro(cyclopentane - 1,1' - indane) (5 g; 0.015 moles), sodium hydroxide (20 g), water (15 ml.) and methanol (15 ml.) are mixed and refluxed for 48 hours. The methanol is then eliminated *in*

vacuo. The alkaline solution is extracted with ether. The ether extract is shaken with 2N hydrochloric acid and then the acid solution is made alkaline with 40% sodium hydroxide and extracted with ether. After drying and evaporation the free amine 3' - β - methylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane) is obtained as a pale oil (2.8 g.).

The perchlorate is obtained if the dry ether solution of the amine is treated with perchloric acid. After recrystallisation from 2-propanol the salt melts at 100°C.

In an analogous manner 3' - β - (N - carbethoxy - N - methylamino) - ethyl - oximino - spiro(cyclohexane - 1,1' - indane) is prepared *via* an oily intermediate.

b) *3' - β - methylaminoethyl - oximino - spiro(cyclohexane - 1,1' - indane).*

Hydrochloride, m.p. 155°C, and *via* the intermediate 1,1' - dimethyl - 3 - β - (N - carbethoxy - N - methylamino) - ethyl-oximino - indane (oil), there is prepared

c) *1,1' - dimethyl - 3 - β - methylaminoethyl - oximino - indane.* Perchlorate, m.p. 135°C.

Example 5.

a) *3' - β - trimethylammonium - ethyl - oximino - spiro(cyclohexane - 1,1' - indane)methylsulphate.*

To 3' - β - dimethylaminoethyl - oximino - spiro(cyclohexane - 1,1' - indane) (8.4 g; 0.03 moles) in methanol (50 ml.) there is added dimethyl sulphate (9 ml.) with shaking. After about 5 minutes, 450 ml. ether are added and crystals of the trimethylammonium compound precipitate (6.8 g; 55%).

After recrystallisation from 2 - propanol/isopropylether the salt melts at 160°C.

In an analogous manner the following quaternary amine salts are prepared from the corresponding tertiary amines:

b) *3' - β - (N,N - diethyl - N - methylammonium)ethyl - oximino - spiro(cyclohexane - 1,1' - indane)methylsulphate.* m.p. 122°C.

c) *3' - β - (N - methyl - 1 - pyrrolidinium)ethyl - oximino - spiro(cyclohexane - 1,1' - indane)methylsulphate.* m.p. 153°C.

Example 6.

3' - β - dimethylaminoethyl - oximino - spiro(cyclohexane - 1,1' - indane) - β - N - oxime hemi - hydrate.

3' - β - dimethylaminoethyl - oximino - spiro(cyclohexane - 1,1' - indane) (2.9 g; 0.026 moles) and methanol (11 ml.) are mixed and kept at room temperature for several days. After evaporation *in vacuo* a glassy mass is obtained which crystallises slowly.

The crystalline product is triturated with isopropyl ether and filtered off giving 6.5 g (Yield 80%) of a colourless product of mp. 44°C.

Example 7.

3' - γ - dimethylaminopropyl - oximino - spiro(cyclopentane - 1,1' - indane)

3' - hydroxyimino - spiro(cyclopentane - 1,1' - indane) (20.1 g; 0.1 moles) in 250 ml of dimethylformamide is converted into the sodium salt by stirring with sodium hydride (4.8 g; 0.1 moles, 50% in paraffin oil). 1,3 - dibromopropane (300 g; 1 mole) is added and then the mixture is heated at 100°C for 24 hours. The excess of dibromopropane and the solvent is distilled off *in vacuo* and the residue is taken up in ether and water. The ether solution is dried with sodium sulphate and evaporated. 3' - γ - bromopropyl - oximino - spiro(cyclopentane - 1,1' - indane) is obtained as an oil. This oil is dissolved in 200 ml of methanol containing 45 g (1 mole) of dimethylamine. The solution is kept in a closed container at room temperature for 14 days and evaporated. The evaporation residue is taken up in ether and water. The ether phase is extracted with 2 N hydrochloride acid, the hydrochloric acid phase washed with ether and made alkaline with 40% sodium hydroxide and then the freed amine is extracted with ether. The extract is dried and the hydrochloride of the amine is precipitated with a solution of hydrogen chloride in ether. After recrystallisation from 2-propanol a colourless product of mp. 186 to 187°C is obtained, which is identical with the product prepared according to Example 2b.

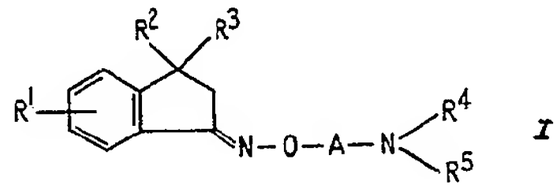
Example 8.

3' - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1' - indane)

A solution of β - dimethylaminoethoxyamine (F. Winternitz and R. Lachazette, Bull. Soc. Chim. France, *1958*. 664) (10.5 g; 0.1 mole) and spiro(cyclopentane - 1,1' - indane)-3' - one (18.6 g; 0.1 mole) in 100 ml of methanol is refluxed for 4 hours. The solution is evaporated *in vacuo* and the residue is taken up in ether. The ether solution is extracted with 2 N hydrochloric acid. The combined acid extracts are washed with ether and made alkaline with 40% sodium hydroxide solution. The freed amine is then extracted with ether. After drying with potassium carbonate the perchlorate is precipitated by the addition of perchloric acid to the ether solution. The salt is filtered off and crystallised from 2-propanol, and then the product melts at 136 to 138°C. The product is identical with the product prepared according to Example 2a.

WHAT WE CLAIM IS:—

1. A 1,1 - disubstituted indane - 3 - one oxime derivative of formula:



I

wherein R^1 represents hydrogen, halogen, an alkoxy group containing 1 to 3 carbon atoms or the nitro group; R^2 and R^3 each represents an alkyl group containing 1 to 3 carbon atoms which may be joined to form together with the carbon atom in the indane ring to which they are bonded, a ring; A represents an ethylene or trimethylene group or an ethylene or trimethylene group which is substituted by a lower (as hereinbefore defined) alkyl group; and R^4 and R^5 each represents hydrogen or an alkyl group containing 1 to 4 carbon atoms or R^4 and R^5, together with the amine nitrogen, form a heterocyclic ring, which in addition to the amine nitrogen may contain an oxygen atom or an imino group which may be substituted by a lower alkyl group; and the amine oxides, quaternary ammonium compounds and salts with physiologically acceptable acids thereof.

2. A compound according to claim 1, wherein R^2 and R^3 each represents a methyl group or, together with the carbon atom to which they are bonded, form a carbocyclic ring.

3. A compound according to claim 2, wherein the carbocyclic ring is a cyclopentane or cyclohexane ring.

4. A compound according to any one of claims 1 to 3, wherein R^1 represents halogen.

5. A compound according to claim 4, wherein the halogen is chlorine or fluorine.

6. 3′ - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1′ - indane).

7. 3′ - β - dimethylaminoethyl - oximino - spiro(cyclohexane - 1,1′ - indane).

8. 5′ - chloro - 3′ - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1′ - indane).

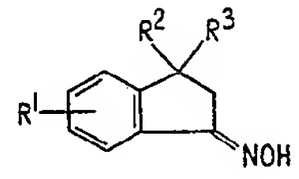
9. 5′ - fluoro - 3′ - β - dimethylaminoethyl - oximino - spiro(cyclopentane - 1,1′ - indane).

10. 3′ - β - methylaminoethyl - oximino - spiro(cyclopentane - 1,1′ - indane).

11. 2,2 - dimethyl - 3 - β - methylaminoethyl - oximino - indane.

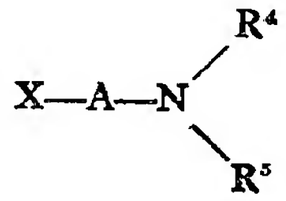
12. A compound or salt as claimed in claim 1, specifically named herein.

13. A process for preparing a compound as defined in any one of the preceding claims, which comprises reacting an indanone oxime of formula:



II

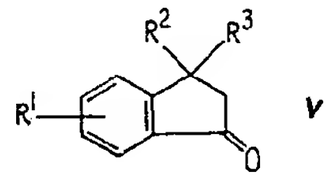
wherein R^1, R^2 and R^3 are as defined in claim 1, with a compound of formula:



III

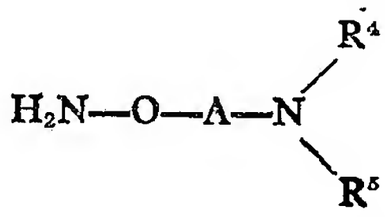
wherein X signifies a reactive ester residue and A, R^4 and R^5 are as defined in claim 1.

14. A process for preparing a compound as defined in any one of claims 1 to 12, which comprises reacting an indanone of formula:



V

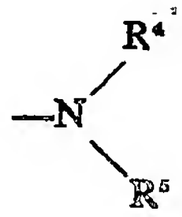
wherein R^1, R^2 and R^3 are as defined in claim 1, with a compound of formula:



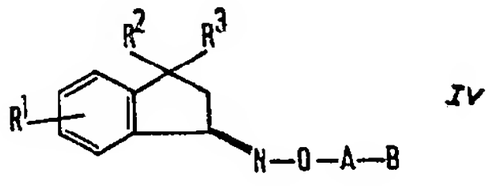
VI

where A, R^4 and R^5 are as defined in claim 1.

15. A process for preparing a compound as defined in any one of claims 1 to 12, which comprises converting in a manner known *per se*, the group B into the group

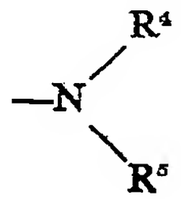


in a compound of formula:



IV

wherein R^1, R^2, R^3 and A are as defined in claim 1, and B signifies a group convertible in manner known *per se* into the group



as defined in claim 1.

16. A process according to claim 15, wherein the group B represents halogen, a protected amino group, a hydroxy group, a nitro group or an alkoxycarbonylamino group.

17. A process according to any one of claims 13 to 16 where the compound of formula I is a primary or secondary amine and the primary or secondary amine is alkylated to a secondary, or tertiary amine or a quaternary ammonium compound.

18. A process according to any one of claims 13 to 16, wherein the compound of formula I is a tertiary amine and the tertiary amine is dealkylated in a manner known *per se* to the corresponding secondary amine.

19. A process according to any one of claims 13 to 18, wherein a halogeno, nitro or C_1—C_3 alkoxy group is introduced in a manner known *per se* into the benzene ring of a reactant of formula II, IV or V or a compound of formula I wherein R^1=H.

20. A process according to any one of claims 13 to 19, wherein a compound of formula I is converted into a salt by reaction with a physiologically acceptable acid.

21. A process according to any one of claims 13 to 20, wherein a compound of formula I is converted in a manner known *per se* into an amine oxide.

22. A process according to any one of claims 13 to 21, wherein a compound or salt of formula I having an asymmetric centre is resolved into its optical antipodes.

23. A process according to any one of claims 13 to 22, substantially as described in any one of Examples 2 to 8.

24. A process according to any one of claims 13 to 22 substantially as hereinbefore described.

25. A compound or salt prepared by a process as claimed in any one of claims 13 to 24.

26. A pharmaceutical composition comprising at least one compound or salt according to any one of claims 1 to 12 or 25, together with a pharmaceutically acceptable carrier or diluent.

27. A composition according to claim 26, in unit dose form.

28. A composition according to claim 27, wherein the unit dose contains 1 mg. to 500 mg. of the compound.

29. A composition according to claim 28, substantially as hereinbefore described.

J. A. KEMP & CO.,
Chartered Patent Agents,
14, South Square,
Gray's Inn, London, W.C.1.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1976.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.